Public Health and Safety

NIST's Role in Healthcare Measurements

NIST

High Accuracy Methods | **Standard Reference Materials, Data and Other QA Services** | **New Measurement Tools**

NIH CDC FDA

AACC AOAC CAP NCCLS

Medical/Clinical Manufacturers

Medical Research Community

Healthcare Delivery

Improved Measurement Accuracy → **Better Diagnoses and Reduced Costs**

Assessing, Prioritizing, and Addressing Measurement Needs

Healthcare

Relevance: Accurate measurement technology and SRMs to support measurement accuracy and traceability are needed for important clinical health status markers.

For example: Cardiac troponin-I is a new definitive biomarker of heart attack not being effectively utilized due to measurement problems)

Example of Variability of Results Among Currently Used Clinical Immunoassays:

Results of Measurements of Troponin-I from Same Sample Pool Using Immunoassay Kits from Three Different Manufacturers

Assay Manufacturer	Troponin-I Concentration ng/mL	# labs reporting
"A"	19.9	115
"B"	6.7	489
"C"	0.85	27

From G. S. Bodor, Denver Health and Hospitals -- personal communication 1997

"Failure to use effective treatments . . . for acute myocardial infarction for all patients who could benefit from these interventions may lead to as many as 18,000 preventable deaths each year in the United States." *- JAMA, 280, 1000, Sept.16, 1998.*

Results:

- Working/conducting workshops with the American Association for Clinical Chemistry (ACC), the Centers for Disease Control and Prevention (CDC) and other similar organizations and with representatives of medical/clinical manufacturers and medical research community to assess needs and prioritize SRM development activities.
  - For example: NIST Workshops with major U.S. *in vitro* diagnostic device (IVDD) manufacturers to address their need to meet requirements of an European Community directive, scheduled to be implemented December 2003, specifically requiring that products sold in Europe be traceable to "standards of the highest order", e.g., nationally/internationally recognized certified reference materials.
- Troponin-I:
  - Developed/published on-line precolumn affinity chromatography-capillary electrophoresis method for the measurement of cardiac troponin I in serum
  - Established method to chemically characterize purified troponin-I preparation
  - Producing cardiac troponin-I SRM; 12 materials being evaluated by NIST and AACC-coordinated group of laboratories to identify material most appropriate for use as SRM
- Developing reference methods for additional health-care biomarkers such as glycated hemoglobin (diabetes), serum throxine (thyroid function), and cortisol (endocrine function)

Food/Nutrition

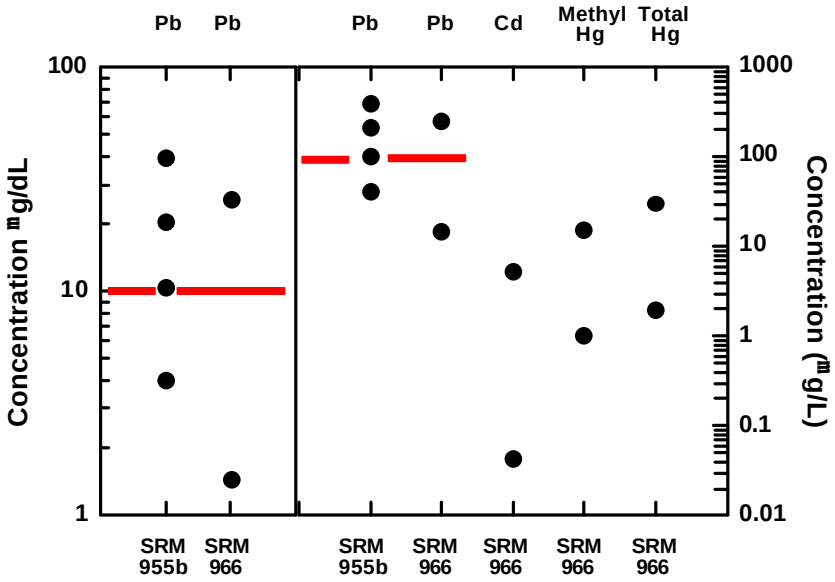
Relevance: Accurate measurement technology and appropriate food SRMs are needed to facilitate compliance with nutritional labeling laws, to provide traceability for food exports needed for acceptance in many foreign markets, and to improve the accuracy of nutrition information that is provided to assist consumers in making sound dietary choices.

Results:

- Working/conducting workshops with members of the National Food Processors Association, AOAC, U. S. Department of Agriculture and other similar organizations to assess needs and prioritize NIST measurement science and SRM development activities.

  – E.g., September 1999 NIST Workshop “Primary Reference Materials Needs for the Food Industry”(in conjunction with AOAC meeting)

Development of SRMs for Toxic Elements in Whole Blood



Project Description: To provide whole blood reference materials with certified concentration values for selected toxic trace metals. These SRMs will benchmark clinical analyses in research and health laboratories.

Results: ID-ICPMS analyses have been used to accurately characterize the concentration of endogenous lead at four different levels in SRM 955b, *Lead in Bovine Blood*. SRM 966 is a new bovine whole blood with two different levels of organically bound lead, spiked cadmium and spiked mercury, both methyl (MeHg) and inorganic forms (Hg++) that was characterized using GC-atomic emission spectrometry as well as ID-ICPMS. The range of analyte concentrations in these two reference materials spans five orders of magnitude, from ppb to sub-ppt.

Relevance: The four elevated levels of lead in SRM 955b provide quality assurance for clinical measurements critical for detecting childhood lead poisoning. The two levels of toxic metals in SRM 966 encompass the ranges commonly observed for real world concentrations of these analytes in whole blood and will provide a traceability link for accuracy in such measurements.

Chemical Measurement Technologies:

- Providing definitive method measurements for 12 health diagnostic markers
- Developing reference methods for additional health-care biomarkers such as glycated hemoglobin (diabetes), serum throxine (thyroid function), and cortisol (endocrine function)
- Improved methods for polyunsaturated fatty acids using chemical ionization/ion trap-MS
- Developed/published on-line pre-column affinity chromatography-capillary electrophoresis method for the measurement of cardiac troponin I in serum
- Developing techniques for characterization and quantitative determination of proteins in biological matrices
- Continued chiral separation research on LC, CE, and GC separation strategies for optical isomers of pharmaceutical and agricultural interest
- Developed techniques to assess the structural heterogeneity of monoclonal antibodies – a factor that can affect the accuracy of immunoassay diagnostic testing
- Developed method for determination of gunpowder additives
- Developed radiochemical method to determine Cd in human blood at natural levels

Standards Development and Quality Assurance Activities:

- Issuing Toxic Elements in Blood SRM and developing new Cardiac Troponin-I standard (new definitive biomarker of heart attack)
- Providing certified values for vitamins, minerals, fat (as fatty acids) and proximates in new food matrix SRMs to support measurements for new nutritional labeling laws (completed meat homogenate; initiated new baking chocolate and spinach matrices
- Value-assigned proximate concentrations in 10 existing food reference materials certified for selected inorganic analytes to support labeling laws.
- Collaborated with College of American Pathologists and the National Institute of Justice to provide standards, proficiency testing and other QA activities supporting accuracy in clinical laboratories and drugs-of-abuse determinations, respectively, and also to those laboratories studying cancer chemopreventive agents,
- Conducted workshops and continuing to assess and prioritize SRM and traceability needs for both health and food/nutrients areas with outside experts from AACC, CDC, USDA, FDA, food companies, relevant trade associations, etc.
- Provided data analysis, value assignment for SRM 2390, RFLP Profiling Standard (all RFLP-measuring forensic laboratories are required to analyze this SRM at least once a year to be eligible to receive federal funding)
- Reissued SRM 955b, Lead in Bovine Blood, which supports the accuracy of >1,000,000 blood lead measurements made on children in the US each year; SRM 968c, Fat Soluble Vitamins and Carotenoids in Human Serum used widely in clinical laboratories; and SRM 1589a, PCBs in Serum and re-certified SRMs 1507-1576, Pb paint films.

Examples of New High-Priority SRMs Under Development

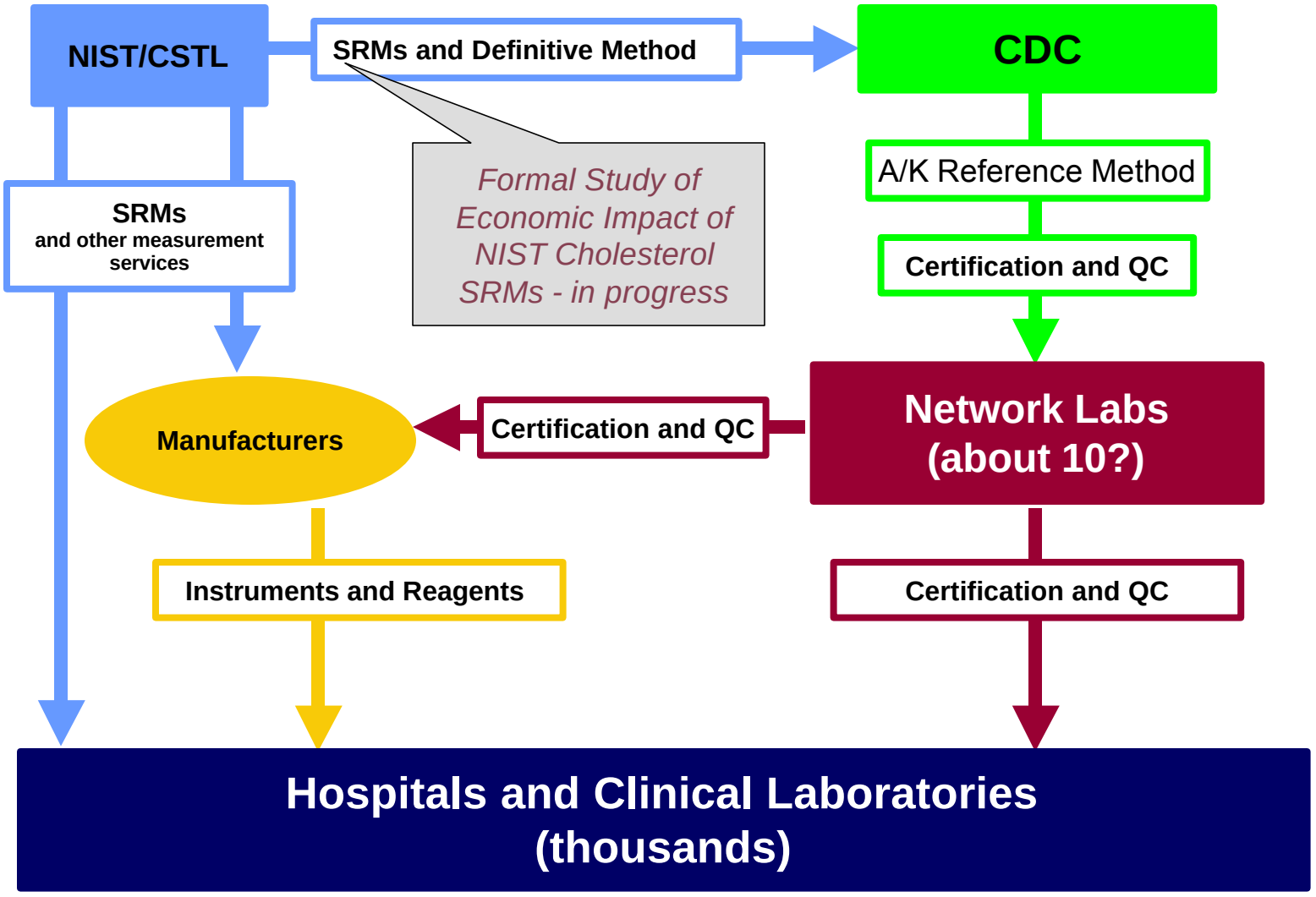
Health

- **Toxic Metals in Blood** (*toxic metals such as Cd, Pb, total mercury, and methylmercury to be certified*)
- **Cardiac Troponin-I** *(new definitive biomarker of heart attack not being effectively utilized due to measurement problems)*
- **Isotopically-depleted Protein Mass Standards** *(with Div. 831) (for use in mass spectrometry)*

Food

- **Baking Chocolate** *(to complement the suite of SRMs developed in response to new nutritional labeling laws)*
- **Frozen Spinach** *(to complement the suite of SRMs developed in response to new nutritional labeling laws)*
- **Fish Fillet** (*toxic contaminants such as PCBs, pesticides, and methylmercury along with food proximates to be certified)*

Cholesterol Reference System



Healthcare Measurements: Measurements for Traceability

To support the national reference system for clinical measurements and the *in vitro* diagnostics device (IVDD) industry

- Maintain and refine definitive methods for 12 health status markers

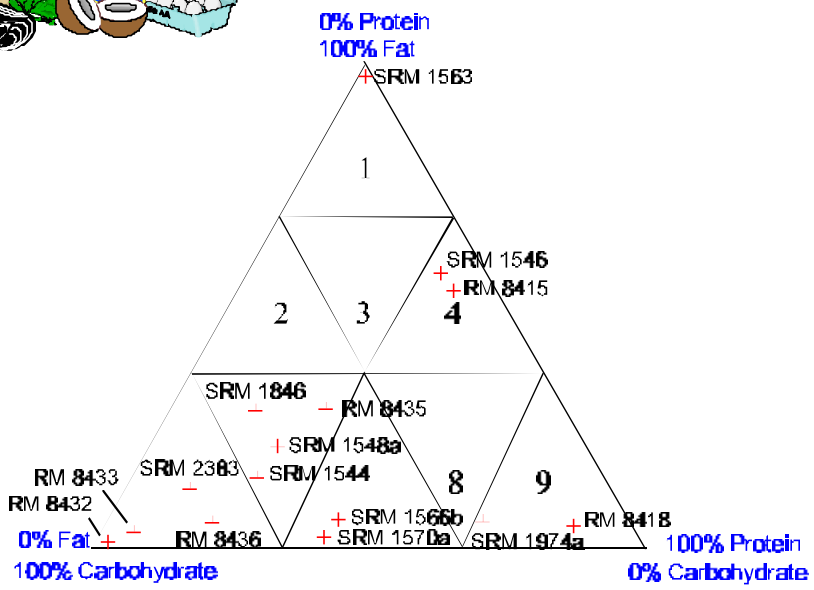
MARKER	*CONDITION*
Calcium	Cancer, Blood Clotting
Chloride	Kidney Function
Cholesterol	Heart Disease
Creatinine	Kidney Function
Glucose	Diabetes
Lithium	Antipsychotic Treatment
Magnesium	Heart Disease
Potassium	Electrolyte Balance
Sodium	Electrolyte Balance
Triglycerides	Heart Disease
Urea	Kidney Function
Uric Acid	Gout

- Develop measurement technology and provide SRMs for new clinical markers

  - Highest priorities/new standards needs:

MARKER	*CONDITION*
Troponin-I	Myocardial Infarction
Glycated Hemoglobin	Diabetes Status
Homocysteine	Risk of Heart Disease
p53 DNA	Breast Cancer
Thyroid stimulating hormone (TSH)	Thyroid Function
Speciated iron	Hemochromatosis, Anemia
Human serum albumin	Renal Failure
Prostate specific antigen (PSA)	Prostate Cancer
Cadmium & Mercury	Toxic Metal Poisoning
Cortisol	Endocrine Function
Thyroxine	Thyroid Function
Folic Acid	Neural Tube Defects

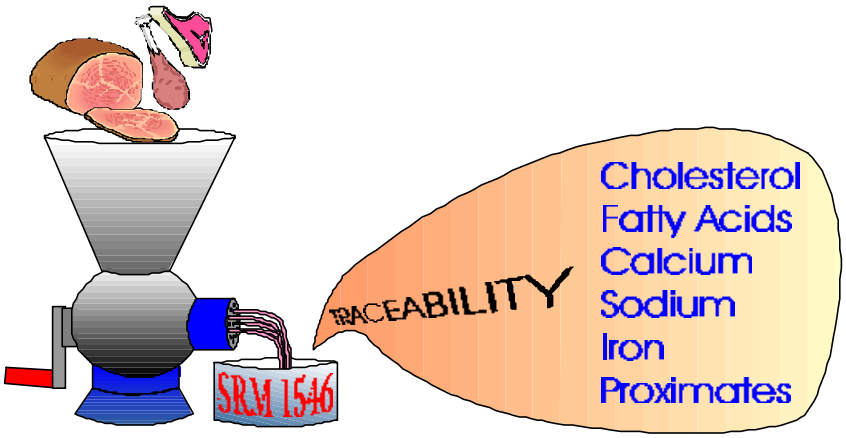
Strategic Selection of Food-Matrix SRMs



SRM 1544 = Fatty Acids and Cholesterol in a Frozen Diet Composite
SRM 1546 = Meat Homogenate
SRM 1548a = Typical Diet
SRM 1563 = Coconut Oil
SRM 1566b = Oyster Tissue
SRM 1570a = Spinach Leaves (Freeze-dried)
SRM 1846 = Infant Formula
SRM 1974a = Mussel Tissue
SRM 2383 = Baby Food Composite
RM 8415 = Whole Egg Powder
RM 8418 = Wheat Gluten
RM 8432 = Corn Starch
RM 8433 = Corn Bran
RM 8435 = Whole Milk Powder
RM 8436 = Durum Wheat Flour

- AOAC International has developed a nine-sectored triangle in which foods are positioned based on their fat, protein, and carbohydrate content.
- AOAC's belief is that one or two reference materials within each sector should be representative of other foods within that sector and could be used for quality assurance, method validation, and providing traceability for analysis of other foods within the same sector.
- NIST is actively working to provide SRMs within each sector with values assigned for proximates (procedurally defined values for fat, protein, carbohydrate, etc.), fatty acids, cholesterol, vitamins, elements of nutritional interest, etc.

Certification of a Meat Homogenate SRM



Project Description: Food producers and government regulators identified a need for a uniform canned meat product to serve as a reference material for components of fat, important minerals, and proximates. A commercially available product was prepared specifically for this SRM. A combination of NIST measurements and results from a large number of laboratories making nutrition measurements was used for the certification. This high fat, high protein material will complement the high carbohydrate (Food Composite, Baby Food, and Infant Formula) and low protein, high fat (Cholesterol in Coconut Oil) SRMs currently available.

Results: Issued SRM 1546: Cholesterol, 6 fatty acids, sodium, calcium, and iron were certified. Reference values were provided for 27 additional constituents including total protein, total fat, carbohydrate, water, ash, calories, and other nutrients.

Relevance: Improved accuracy and traceability in nutrition labeling leads to better informed consumers and acceptance of U.S. food products in world markets.